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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/081,522	05/19/1998	PETER BROOKS	TSRI419OCONI	1607

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/17/2003

27

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/085,512	BROOKS
Examiner	**Art Unit**
GAMBEL	1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 11/4/02

2a)☑ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) ____ is/are pending in the application. 171-188, 205-286

4a) Of the above claim(s) ____ is/are withdrawn from consideration

5)☐ Claim(s) ____ is/are allowed.

6)☑ Claim(s) ____ is/are rejected. 171-188, 205-286

7)☐ Claim(s) ____ is/are objected to.

8)☐ Claim(s) ____ are subject to restriction and/or election requirement

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on ____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on ____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. ____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
4)☐ Interview Summary (PTO-413) Paper No(s). ____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

PAPER NO. 27

DETAILED ACTION

1. Applicant's amendment, filed 12/14/02 (Paper No. 25), has been entered.
Claims 189-204 have been canceled. Claims 1-170 have been canceled previously.

Claims 171-188, 205-286, as they read methods of inhibiting breast cancer of treatment with $\alpha_v\beta_3$-specific antibodies / LM609-specific antibodies are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 12/14/02 (Paper No. 25).
The rejections of record can be found in the previous Office Action (Paper No. 23).

3. Claims 171-188, 205 -286 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kim (WO 93/20229; 1449) AND/OR Cheresh (WO 89/05155; 1449) in view of Nicosia et al. (Am. J. Pathol. 138: 829 - 833, 1991; 1449), Nip et al. (J. Clin. Invest. 90: 1406-1413, 1992; 1449) , Folkman et al. (Seminars in Cancer Biology 3: 89-96, 1992; 1449), Pignatelli et al. (Hum Pathol 23:1159-1166 (1992) and conventional or art known procedures to treating cancers of interest at the time the invention was made, as taught by the references set forth herein or acknowledged on pages 13-23 of the instant specification for the reasons of record set forth in Paper No. 23.

Applicant's arguments, filed 12/14/02 (Paper No. 25), have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues that the cited references fail to teach or suggest the claimed invention, that the cited references do not provide sufficient motivation or expectation of success and that the cited references teach away from the claimed invention.

Applicant asserts that Kim et al. and Cheresh et al. at best teach αvβ3-specific antibodies that can inhibit melanoma tumor growth and metastasis because tumor growth depends on cell attachment but that Kim et al. and Cheresh et al. do not teach targeting breast cancer.

Applicant notes that Kim et al. explicitly teach that αvβ3-specific antibodies could not be used to treat tumor cells that do not bind the antibody (Kim at page 9, lines 12-14).

Applicant asserts that neither Kim nor Cheresh disclose or suggest using αvβ3-specific antibodies for treating specific types of patients, such as those previously treated for a tumor.

Applicant asserts that there is no evidence in the references that the tumor-inhibiting amounts in mouse melanoma model an any way encompasses an angiogenesis-inhibiting amounts. Further applicant asserts that tumor inhibiting amounts alleged/proposed in the art for a particular type of tumor and/or patient have no correlation whatsoever to the angiogenesis-inhibiting amount for different type of tumor in a different patient of vice versa. Applicant asserts that methods encompassing administering the tumor-inhibiting amounts to one type of tumor cell and/or patient are wholly irrelevant and suggest nothing about angiogenesis-inhibiting amounts administered to a different type of tumor cell and/or patient.

Applicant asserts that the secondary references do not cure the defects of the primary references and actually teach away from the claimed invention.

Applicant asserts that the experimental results reported in Pignatelli not only failed to cure the deficiencies of the cited primary references but teach away from the use of $\alpha v\beta 3$ as a target for treating breast cancer. Applicant notes that the data provides in Tables 2-3 on pages 1163-1164 of Pignatelli demonstrate that $\alpha v\beta 3$ in only weakly expressed in 50% of the invasive lobular carcinomas characterized and only weakly expressed in one of the nineteen invasive ductal carcinomas. In turn, applicant asserts that non-existent or weak expression of $\alpha v\beta 3$ in comparison to other integrins in carcinomas as reported by Pignatelli suggest that the ordinary artisan that $\alpha v\beta 3$ would not play a role in the progression of invasive breast carcinomas as would other more highly expressed integrins.

Applicant asserts that Nip, like Cheresh and Kim reports on in vitro studies exploring activity of $\alpha v\beta 3$-specific antibodies for targeting melanoma. Applicant asserts that Nip reports the incidence and growth rate of primary tumors were unaffected by treatment with $\alpha v\beta 3$-specific antibodies (page 1408, Nip et al.).

Applicant asserts that Nicosia does not teach or suggest that $\alpha v\beta 3$-specific antibodies could be used to inhibit angiogenesis and does not teach target breast cancer cells or preventing / inhibiting solid tumor growth or metastasis.

Applicant notes that Folkman reviews the use of angiogenesis as possible anti-cancer therapy. Applicant asserts that Folkman does not teach $\alpha v\beta 3$-specific antibodies as anti-angiogenic and provides no expectation of success.

Applicant argues that not only do the primary and secondary references fail to suggest claimed invention obvious, there is no motivation for the asserted combination of primary and secondary references.

Applicant notes that the examiner indicates that certain claimed limitations such as specific dosages or modes of administration were conventional at the time the invention was made. Applicant asserts such conclusory statements are insufficient to support a rejection

One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992). In this case the combined teachings provide sufficient motivation and expectation of success to target αvβ3 expressing breast cancer cells with αvβ3-specific antibodies and that such αvβ3-specific antibodies would have been administered in angiogenesis-inhibiting amounts for the reasons of record and addressed herein. Therefore, the combined teachings do provide sufficient motivation and expectation of success to solve a similar problem encompassed by the instant methods. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

With respect to applicant's assertions on teaching away, a prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley , 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc. , 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness. See MPEP 2123.

In contrast to applicant's assertions, there is no teaching away by the references of the prior art.

Although the Kim and Cheresh references do not state an "angiogenesis-inhibiting amount" per se; the tumor-inhibiting amount taught by the reference would intrinsically or expectedly encompass the "angiogenesis-inhibiting amount" encompassed by the claimed methods.

With respect to applicant's assertions concerning angiogenesis-inhibiting amounts, pages 9-10 of Kim disclose dosages and modes of administration based upon the severity of the disease, including dosages of about 0.015 mg to 15 mg of antibody/Kg of patient weight.

In a similar fashion, Cheresh discloses therapeutic dosages can be administered in a manner compatible withe patient and disease targeted to achieve a therapeutic amount (see pages 22-23). Suitable dosages range in the order of 0.1 to 10 mg, which can be modified based on the therapeutic regimen.

This is consistent with the instant disclosure that indicates that the therapeutic effects amounts depends upon the form of the antagonist which will depend on the nature of disease and patient and can be determined by the ordinary artisan (e.g. see page 17, paragraph 1 of the instant specification). Page 19, paragraph 1 of the instant specification discloses dosages, including a wide range of dosages, that are consistent with the prior art. The prior art dosages are not limited to specific examples employed in experimental models. Further, it is noted that the instant claims either do not recite a specific dosage amount or recite a broad dosage range of about 0.1 mg to about 300 mg/kg body weight".

In addition to the conventional or art known procedures, including dosages, modes of administration and regimens in order to meet the needs of the patients and to inhibit tumor growth to treating cancers of interest at the time the invention was made, as taught by the references set forth herein (e.g. pages 9-10 of Kim) or acknowledged on pages 13-23 of the instant specification.

In contrast to applicant's assertions concerning the expression of $\alpha v\beta 3$ on breast cancer cells, Pignatelli et al. identified changes with with αv integrins on breast epithelia during malignant transformation and identified the integrin with $\alpha v\beta 3$ in a high percentage of invasive lobular carcinomas in breast cancer patients (see entire document, including Abstract and Discussion). Pignatelli et al. also state that overexpression of integrin molecules mediating cell migration such as $\alpha v\beta 3$ may allow the tumor cells to invade the adjacent tissued and vascular channels and contribute to metastasis as shown in malignant melanomas (page 1164, column 2). Pignatelli et al. further states that the detection of αv chain in poorly differentiated carcinomas is highly suggestive of a similar role played by the vitronectin receptor in the progression of invasive breast carcinomas and that the finding that $\alpha v\beta 3$ is expressed in more ILCs than IDCs has some significance in the differing biologic behavior of these cell types (see page 1164, column 2, lines 25-33).

As pointed out previously, the following is noted.

Kim teaches neutralizing antibodies, including humanized and antibody fragments, that bind αvβ3, including the LM609 antibody, that inhibit binding tumor cells with vitronectin, fibrinogen and von Willebrand factor in vivo, in order to inhibit tumor growth and metastasis because tumor growth depends on cell attachment, (see entire document, including Background of the Invention, Summary of the Invention, and Detailed Description of the Invention; also, see page 6, paragraph 2; page 9, paragraph 2)

Kim also teaches modes of administration and doses of therapeutic antibody alone or in combination with other agents that are effective for the same clinical objective, depending on the type of the disease, the severity and course of the disease in the individual at the discretion of the practitioner (pages 9-10); wherein said modes of administration and doses are encompassed by the claimed methods

Although the Kim and Cheresh references do not state an "angiogenesis-inhibiting amount" per se; the tumor-inhibiting amount taught by the reference would intrinsically or expectedly encompass the "angiogenesis-inhibiting amount" encompassed by the claimed methods.

With respect to applicant's assertions concerning angiogenesis-inhibiting amounts, pages 9-10 of Kim disclose dosages and modes of administration based upon the severity of the disease, including dosages of about 0.015 mg to 15 mg of antibody/Kg of patient weight.

In a similar fashion, Cheresh discloses therapeutic dosages can be administered in a manner compatible withe patient and disease targeted to achieve a therapeutic amount (see pages 22-23). Suitable dosages range in the order of 0.1 to 10 mg, which can be modified based on the therapeutic regimen.

This is consistent with the instant disclosure that indicates that the therapeutic effects amounts depends upon the form of the antagonist which will depend on the nature of disease and patient and can be determined by the ordinary artisan (e.g. see page 17, paragraph 1 of the instant specification). Page 19, paragraph 1 of the instant specification discloses dosages, including a wide range of dosages, that are consistent with the prior art.

In addition to the conventional or art known procedures, including dosages, modes of administration and regimens in order to meet the needs of the patients and to inhibit tumor growth to treating cancers of interest at the time the invention was made, as taught by the references set forth herein (e.g. pages 9-10 of Kim) or acknowledged on pages 13-23 of the instant specification

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art . In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969).

In this case, one of ordinary skill in the art at the time the invention was made would have been motivated to select αvβ3/ RGD-specific inhibitors such as αvβ3-specific antibodies such as the LM609 specificity to inhibit tumor growth and metastasis in combination with conventional therapy to treat cancer. Providing αvβ3-specific antibodies such as the LM609 in "angiogenesis-inhibiting amounts" encompassed by the claimed methods would have been expected; given the prior art teaching of inhibiting tumor growth and metastasis. Again while the primary references do not state an "angiogenesis-inhibiting amount" per se; the tumor-inhibiting amount taught by the reference would have the expected properties of an "angiogenesis-inhibiting amount" encompassed by the claimed methods; given the combined teachings of inhibiting tumor growth and metastasis with αvβ3/ RGD-specific inhibitors, including the LM609 and RGD inhibitors inhibit angiogenesis. In contrast to applicant's assertions, the secondary references provide a sufficient nexus of angiogenesis or angiogenesis -inhibiting amounts with αvβ3/ RGD-specific inhibitors and tumor growth and metastasis. For example, Nicosia et al. teach inhibiting angiogenesis by a RGD inhibitor (see entire document, including the Abstract). Also, it was known at the time the invention was made that angiogenesis was necessary but not sufficient for expansion of tumor population, as taught by Folkman et al. (See entire document, particularly Rationale of anti-angiogenic therapy on page 89). Folkman et al. Also teach that angiogenesis inhibitors may be administered to cancer patients in conjunction with convention chemotherapy for the control of metastatic disease such as prostate, breast or colon cancer (see page 94, column 1, paragraph 3). Also, given the metastatic behavior of various tumors, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply such therapeutic intervention to target various tumor types, including those from bladder, breast, colon or lung. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

4. No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
March 14, 2003